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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/697,703	10/31/2003	H. William Bosch	029318-0973	8369

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EXAMINER	
CLARK, SARA E	

ART UNIT	PAPER NUMBER
1613	

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11/09/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/697,703	BOSCH ET AL.	
	Examiner	Art Unit	
	SARA E. CLARK	1613	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 July 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-95* is/are pending in the application.

4a) Of the above claim(s) *12, 13, 27, 32-35, 39, 41-43, and 45-95* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11,14-26,28-31,36-38,40 and 44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/4/2010 and 4/9/2010*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

NON-FINAL REJECTION

In view of the Appeal Brief filed on 7/29/2010, PROSECUTION IS HEREBY REOPENED. New grounds of rejection are set forth below.

To avoid abandonment of the application, appellant must exercise one of the following two options:

(1) file a reply under 37 CFR 1.111 (if this Office action is non-final) or a reply under 37 CFR 1.113 (if this Office action is final); or,

(2) initiate a new appeal by filing a notice of appeal under 37 CFR 41.31 followed by an appeal brief under 37 CFR 41.37. The previously paid notice of appeal fee and appeal brief fee can be applied to the new appeal. If, however, the appeal fees set forth in 37 CFR 41.20 have been increased since they were previously paid, then appellant must pay the difference between the increased fees and the amount previously paid.

A Supervisory Patent Examiner (SPE) has approved of reopening prosecution by signing below:

/Brian-Yong S Kwon/

Supervisory Patent Examiner, Art Unit 1613

Status of the Claims

Applicant's responses dated 2/26/2007 and 8/21/2007 in response to the requirement for Restriction/Election are summarized as follows. Group I (claims 1-44) drawn to a nimesulide composition was elected without traverse. Applicant further elected five species:

- crystalline as the phase of nimesulide;
- oral as the route of administration;
- tablet as the dosage form;
- random copolymer of vinyl acetate and vinyl pyrrolidone (a.k.a. PVP/VA, Plasdone® S-630) as the non-ionic surface stabilizer;
- analgesics, specifically codeine, as the non-nimesulide active agent.

Thus, Groups II and Group III (claims 45-95), are withdrawn as directed to non-elected inventions. Claims 12 and 13 are withdrawn as drawn to non-elected surface stabilizers. Claim 27 is withdrawn as drawn to a non-elected additional component comprising nimesulide having a different particle size. Claims 32-35 are withdrawn as directed to non-elected dosage form. Claims 39 and 41- 43 are withdrawn as directed to non-elected non-nimesulide active agents.

Therefore, claims 1-11, 14-26, 28-31, 36-38, 40 and 44 are examined on the merits as reading on the elected species.

INFORMATION DISCLOSURE STATEMENT

The information disclosure statements (IDS) submitted on 3/4/2010 and 4/9/2010 were filed after the mailing date of the Office Action on 2/18/2010. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statements have been considered by the examiner.

WITHDRAWN REJECTIONS

Rejections under 35 USC §103

A. Claims 1-15 and 27-31 stand rejected under 35 U.S.C. 103(a) as being unpatentable over REINER et al. (USPN 5,711,961) in view of RYDE et al. (USPN 6,375,986).

The text of the rejection set forth in the Office Action dated 12/9/2008 is incorporated herein by reference.

B. Claims 1, 10-13, and 15-26 stand rejected under 35 U.S.C. 103(a) as being unpatentable over REINER and RYDE in view of LIVERSIDGE et al. (USPN 5,552,160).

The text of the rejection set forth in the Office Action dated 12/9/2008 is incorporated herein by reference.

C. Claims 1 and 16-26 stand rejected under 35 U.S.C. 103(a) as being unpatentable over REINER and RYDE in view of SINGH et al. (Analytical Profiles of Drug Substances and Excipients, Volume 28, 2001, p. 197-249) and BOSCH et al. (USPN 5,510,118).

The text of the rejection set forth in the Office Action dated 12/9/2008 is incorporated herein by reference.

D. Claims 1, 36-38, and 40 stand rejected under 35 U.S.C. 103(a) as being

unpatentable over REINER and RYDE in view of SINGH et al. and MERCK (The Merck Index 12th ed. Merck & Co. 1996, p. 416-417).

The text of the rejection set forth in the Office Action dated 12/9/2008 is incorporated herein by reference.

E. Claims 1 and 44 stand rejected under 35 U.S.C. 103(a) as being unpatentable over REINER and RYDE in view of BUHL et al. (USPN 5,776,563).

The text of the rejection set forth in the Office Action dated 12/9/2008 is incorporated herein by reference.

NEW REJECTIONS

Claim Rejections - 35 USC § 103

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. Claims 1-11, 14-26, 28-31, and 44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Liversidge et al. (USPN 5,552,160, cited on the IDS dated 4/1/2004) in view of Singh et al. (USPN 6,017,932).

Liversidge et al. disclose pharmaceutical compositions which exhibit reduced

gastric irritation and hastened onset of action, comprising dispersible particles consisting essentially of a crystalline NSAID (non-steroidal anti-inflammatory drug) having a surface modifier adsorbed on the surface thereof, in an amount sufficient to maintain an effective average particle size of less than about 400 nm (abstract; col. 1, lines 61-64).

The nanoparticulate NSAID exists in a discrete, crystalline phase, and is poorly soluble (col. 2, lines 39-58). Suitable surface stabilizers do not chemically react with the NSAID and can include, *inter alia*, polyvinyl pyrrolidone (PVP) or tyloxapol (col. 3, lines 57-58; col. 4, lines 10-19). At least 90% of the particles have an average particle size of less than about 400 nm (col. 4, lines 26-27).

The relative amount of the NSAID and the surface modifier can vary widely, and the optimal amount of the surface modifier can depend, for example, upon the particular NSAID and surface modifier selected (col. 6, lines 5-15). Compositions comprising the surface-stabilized nanoparticles can be administered orally, for example, as a liquid dispersion spray-coated onto sugar spheres (col. 6, line 56 to col. 7, line 11).

Liversidge et al. exemplify compositions comprising proportions of NSAID to surface modifier (naproxen, Examples 1-2; ibuprofen, Examples 3-8; and indomethacin, Examples 9-12) falling within the ranges recited by claims 7 and 8. Also disclosed are examples of suitable excipients which can be included in the compositions are disclosed (col. 3, lines 34-56), noting that two or more surface modifiers can be used in combination, as recited by claim 9. The composition can be considered bioadhesive

because the surface modifiers adhere to the surface of the NSAID, but do not chemically bond to the NSAID (see col. 3, lines 25-27), as recited by claim 15.

Further, the nanoparticulate NSAID compositions of Liversidge et al. have decreased T_{max}, increased C_{max}, and increased AUC, when compared to larger particles (see col. 9, lines 1-20), as recited by claims 16-21, 25, and 26. In particular, the size of the control particles was between 20-30 microns (col. 7, lines 35- 38), while the size of the nanoparticles was between 240-300 nm (col. 7, lines 32-34). A simple screening process was used to determine compatible surface modifiers with NSAIDs, and also the amounts of surface modifier and NSAID, which can be adjusted by known variables (col. 6, lines 5-55).

However, Liversidge et al. do not expressly identify nimesulide as a suitable NSAID.

Singh et al. disclose pharmaceutical compositions with enhanced bioavailability of non-steroidal anti-inflammatory drugs (NSAIDs), as compared to known compositions, with the benefits of reducing both the dosage required and dose-related side effects (abstract). Preferably, the NSAID is nimesulide, nabumetone, tepoxalin, flosulide and/or derivatives thereof (col. 1, lines 10-12). In particular, Singh et al. exemplify tablets comprising nimesulide and polyvinyl pyrrolidone (PVP, a.k.a. povidone) as an excipient (Examples III, IV, and VI), as recited by claim 5.

One of ordinary skill in the art would have been motivated to modify the compositions disclosed by Liversidge et al. by incorporating nimesulide as the NSAID for several reasons. First, Singh et al. disclose distinct advantages of nimesulide, such

as its better gastric tolerance than other common NSAIDs; high efficacy against cancer pain; and comparable or superior analgesia to other NSAIDs like diclofenac or piroxicam (col. 2, lines 28-36). Singh et al. teach that nimesulide exhibits potency similar to or greater than that of indomethacin, diclofenac, piroxicam and ibuprofen in standard animal models of inflammation; and animal studies have suggested that nimesulide is less ulcerogenic than aspirin, indomethacin, naproxen, piroxicam and ibuprofen (col. 2, lines 44-66).

Liversidge et al. identify nabumetone, diclofenac, piroxicam, indomethacin, ibuprofen, aspirin, and naproxen as suitable NSAIDs (col. 3, lines 1-20). Singh's focus on four specific NSAIDs, including nabumetone and nimesulide, and the particular advantages associated with the latter, strongly suggests to the skilled artisan that nimesulide could be successfully formulated as taught by Liversidge et al.

Thus, nimesulide as taught by Singh et al. formulated as taught by Liversidge et al., having an average particle size of less than 400 nm and a surface modifier such as PVP or tyloxapol adsorbed on the surface thereof, reads on the composition recited by claims 1 and 3. Liversidge et al. disclose that the NSAID is in crystalline form, as recited by claim 2. Both references disclose the oral route of administration, as recited by claim 4; additional excipients, as recited by claim 6; and polyvinylpyrrolidone (PVP), as recited by claims 10 and 11. Liversidge et al. discloses tyloxapol as a preferred surface modifier (col. 3, lines 57-58), as recited by claim 14.

Nimesulide compositions formulated as taught by Liversidge et al. would be reasonably expected to exhibit similarly decreased T_{max} and increased C_{max} and AUC,

when compared to non-nanoparticle formulations of nimesulide, as recited by claims 16-21, 25, and 26. Because products of identical chemical composition cannot have mutually exclusive properties, the compositions of Liversidge et al. as modified by Singh et al. would also be expected to possess the absorption properties recited by claims 22-24, and the redispersal properties recited by claims 28-31. A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the composition, the properties applicant claims are necessarily present. *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990).

While neither reference explicitly discloses sterile-filtered compositions, as recited by claim 44, this limitation is implicit in the disclosed methods of preparing the formulations for administration to humans, since it is well-known in the medicinal arts that pharmaceutical compositions must be free of biological and chemical contaminants in order to be safe and effective.

A skilled artisan would have been motivated to substitute less-ulcerogenic nimesulide as taught by Singh et al. (col. 2, lines 65-67) into the surface-modified NSAID compositions of Liversidge et al. to obtain the advantage of even further reduction of gastric irritation (col. 2, lines 18-19). A skilled artisan would expect the combination to work, because Singh et al. teaches that nimesulide is poorly soluble and dispersible in at least one liquid medium (col. 3, lines 54-61) as required by Liversidge et al. (col. 2, lines 52-54).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to formulate nimesulide, as taught by Singh et

al., as an NSAID nanoparticle with a surface modifier adsorbed thereon, as taught by Liversidge et al. with a reasonable expectation of success, because the references disclose the advantages of improving the bioavailability of poorly-soluble NSAID drugs, hastening the onset of therapeutic effects, and reducing side effects.

3. Claims 1, 36-38, and 40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Liversidge et al. (USPN 5,552,160) in view of Singh et al. (USPN 6,017,932) as applied to claims 1-11, 14-26, 28-31, and 44 above, and further in view of The Merck Index (cited in the previous action).

As discussed above, **Liversidge et al**. disclose pharmaceutical compositions comprising dispersible particles consisting essentially of a crystalline NSAID (non-steroidal anti-inflammatory drug) having a surface modifier adsorbed on the surface thereof, in an amount sufficient to maintain an effective average particle size of less than about 400 nm (abstract; col. 1, lines 61-64).

The nanoparticulate NSAID exists in a discrete, crystalline phase, and is poorly soluble (col. 2, lines 39-58). Suitable surface stabilizers do not chemically react with the NSAID and include, *inter alia*, polyvinyl pyrrolidone (PVP) and tyloxapol (col. 4, lines 10-19). At least 90% of the particles have an average particle size of less than about 400 nm (col. 4, lines 26-27).

However, Liversidge et al. do not expressly identify nimesulide as a suitable NSAID.

Singh et al. disclose pharmaceutical compositions with enhanced bioavailability of non-steroidal anti-inflammatory drugs (NSAIDs), as compared to known compositions of the drugs, with the benefits of reducing both the dosage required and dose-related side effects (abstract). Preferably, the NSAID is nimesulide, nabumetone, tepoxalin, flosulide and/or derivatives thereof (col. 1, lines 10-12). In particular, Singh et al. exemplify tablets comprising nimesulide and polyvinyl pyrrolidone (PVP, a.k.a. povidone) as an excipient (Examples III, IV, and VI), as recited by claim 5.

Liversidge et al. identify nabumetone, diclofenac, piroxicam, indomethacin, ibuprofen, aspirin, and naproxen as suitable NSAIDs (col. 3, lines 1-20). Singh's focus on four specific NSAIDs, including nabumetone and nimesulide, and the particular advantages associated with the latter, strongly suggests to the skilled artisan that nimesulide could be successfully formulated as taught by Liversidge et al. Thus, nimesulide as taught by Singh et al. formulated as taught by Liversidge et al., having an average particle size of less than 400 nm and a surface modifier such as PVP or tyloxapol adsorbed on the surface thereof, reads on the composition recited by claim 1.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to formulate nimesulide, as taught by Singh et al., as an NSAID nanoparticle with a surface modifier adsorbed thereon, as taught by Liversidge et al. with a reasonable expectation of success, because the references disclose the

advantages of improving the bioavailability of poorly-soluble NSAID drugs, hastening the onset of therapeutic effects, and reducing side effects.

However, Liversidge et al. and Singh et al. do not disclose compositions further comprising a non-nimesulide active agents specifically the analgesic codeine, as recited by claims 36-38 and 40.

Singh et al. teach that nimesulide has analgesic properties (col. 2, lines 44-54).

In addition, as disclosed by **Merck**, it is well-known in the art that codeine has analgesic properties (p. 2531, left column). As recognized by MPEP §2144.06, "it is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art." *In re Kerkhoven*, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980).

Here, both nimesulide as disclosed by Singh et al. and codeine as taught by Merck were known to be administered in pharmaceutical compositions to produce analgesia (pain relief). Thus, it would have been predictable to a skilled artisan to combine two analgesics with a reasonable expectation of success.

CONCLUSION

Claims 1-11, 14-26, 28-31, 36-38, 40 and 44 are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SARA E. CLARK whose telephone number is (571) 270-

7672. The examiner can normally be reached on Mon - Fri, 8:30 am - 5:00 pm (EST). If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brian-Yong Kwon, can be reached at 571-272-0581. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/SARA E. CLARK/
Examiner, Art Unit 1613

/Barbara P. Badio/
Primary Examiner, Art Unit 1628